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Photoinduced and *N*-Bromosuccinimide-Mediated Cyclization of 2-Azido-*N*-phenylacetamides

Zhan-Shan Li, Wei-Xia Wang, Ji-Dong Yang, Yue-Wei Wu, and Wei Zhang*

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

zhangwei6275@lzu.edu.cn

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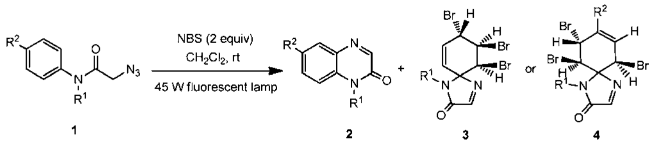
ABSTRACT



An efficient synthesis of quinoxalin-2(1*H*)-ones or spiro[cyclohexene-1,2′-imidazol]-4′-ones has been achieved in moderate to high yields by the visible light-induced and *N*-bromosuccinimide-mediated cyclization reaction of 2-azido-*N*-phenylacetamides at ambient temperature. Both the regioselectivity and the speed of cyclization are affected by the substituents attached to the phenyl ring. For example, quinoxalin-2-ones are produced as the main products when the substrates bear electron-withdrawing groups at the *para*-position of the phenyl ring; in contrast, spiro[cyclohexene-1,2′-imidazol]-4′-ones are obtained as the main products when the substrates bear electron-donating groups at the *para*-position.

Organic azides have been long known as versatile and valuable intermediates in the construction of nitrogen-containing heterocycles. They can be used as progenitors of nitrenes and nitrenium ions in cycloadditions with various dipolarophiles or used as 1,3-dipolar ions to [3 + 2] reaction with alkenes, alkynes, and nitriles for the preparation of heterocycles such as triazoles and tetrazoles.[1] In recent years, great attention has also been devoted to the radical reactions of organic azides.[2] Numerous studies have clearly established that azides, including aliphatic, aromatic, and sulfonyl derivatives, can be transformed to nitrogen-centered radicals.[3] Among these nitrogen-centered radicals, iminyl radicals are of significant interest in synthetic chemistry because they display ability to perform cyclizations onto aromatic rings[4] and double bonds.[5] Iminyl radicals are generally produced by the photolysis or thermolysis of *N*-substituted imine derivatives[4−6] and intramolecular addition of carbon and nitrogen radicals to nitriles.[7] As a complement to these protocols, iminyl radicals can be generated from aliphatic azides via the abstraction of α-hydrogen by carbon radicals[4c] or via the addition of carbon radicals to vinyl azides, followed by nitrogen extrusion.[8] There are studies showing that iminyl radicals are involved in the photoreaction of β-glycosyl azides with *N*-bromosuccinimide (NBS).[9] However, no report has been found to apply this reaction to the synthesis of heterocyclic compounds.

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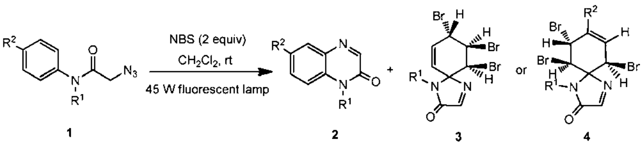
As part of our ongoing venture to develop new synthetic methodologies based on the photochemical reactions of azides,[10] we report herein a new cyclization reaction of iminyl radicals generated by the visible light induced and NBS-mediated reaction of **2**-azido-*N*-phenylacetamides (**1**) (Scheme 1). The reactions afforded two kinds of products, quinoxalin-2-ones (**2**) and spiro[cyclohexen-1,2′-imidazol]-4′-ones (**3** or **4**), in different proportions.

Quinoxalin-2(1*H*)-ones and spiro[cyclohexene-1,2′-imidazol]-4′-ones are important heterocycles displaying a wide range of biological and medicinal activities, and are scaffolds for drug-related molecules. For example, compounds I and II show antithrombotic and antitumor activity;[11] compounds III are glycine transporter inhibitors;[12a] IV are antagonists of CGRP receptors[12b] (Figure 1).

Scheme 1. Photoreaction of 2-Azido-*N*-phenylacetamides with NBS



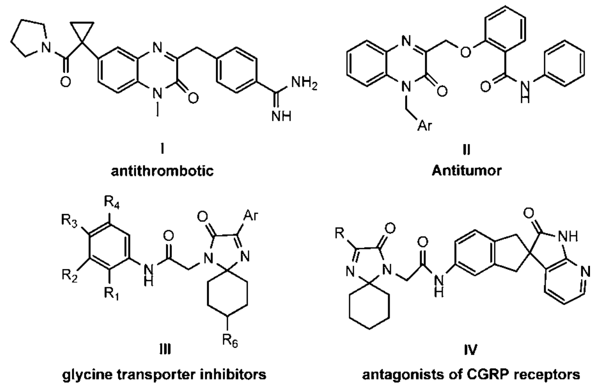


Figure 1. Some pharmaceutically important quinoxalin-2-one and spiro[cyclohexene-1,2′-imidazol]-4′-one derivatives.

Many reports have been found for the synthesis of quinoxalin-2-ones. The traditional methods for assembling quinoxalin-2-ones are based on the condensation of a substituted *o*-phenylenediamine with an α-ketone acid ester or α-aldehyde acid ester.[13a,b] In recent years, a number of new methods have been developed. For example, Bao reported the synthesis of quinoxalin-2-ones by copper-catalyzed cascade reaction of **2**-halo-*N*-(2-halophenyl)-acetamides with $TsNH_2$;[13c] Leardini and Spagnolo reported the synthesis of quinoxalin-2-ones by tributyltin hydride mediated radical cyclization reaction of *o*-iodo-*N*-methylanilides.[13d] Compared with the synthesis of quinoxalin-2-ones, few reports are avaliable concerning the synthesis of spiro[cyclohexene-1,2′-imidazol]-4′-ones and similar compounds. Recently, Chiba and co-workers described a copper-catalyzed synthesis of spiro[cyclohexadiene-1,2′-imidazol]-4,4′-diones by the cyclization of α-azido-*N*-arylamides under an oxygen atmosphere.[14] The new method reported here is an efficient and simple procedure for the synthesis of both quinoxalin-2-ones and spiro[cyclohexadiene-1,2′-imidazol]-4′-ones.

The initial pilot efforts were focused on the optimization of light-induced and NBS-mediated cyclization of 2-azido-*N*-phenylacetamide (**1a**). Previous NBS-related articles suggested the formation of radicals from NBS could be achieved under both UV irradiation[15] and visible light irradiation.[16] It was found, however, that only visible light irradiation was suitable for the cyclization of **1a** to afford **2a** and **3a** in dichloromethane (DCM) at room temperature (Table 1). Under UV irradiation, the reaction resulted in formation of complex products. Control experiment showed that no reaction was detected under reflux in dark in DCM, indicating that irradiation was essential to this reaction. Under visible light irradiation, complete conversion of **1a** could be achieved when 2.0 equiv of NBS was used (entry 3, Table 1). It was noticed that the product **3a** was always detected no matter how much NBS was used (entries 1−3), and the proportion of **2a** and **3a** did not vary greatly, suggesting that **2a** and **3a** were formed at the same time.

Moreover, various solvents were also examined, and DCM proved to be the best choice (entries 3−6, Table 1).

Under the optimal reaction conditions (entry 3, Table 1), the photoreactions of a group of 2-azido-*N*-phenylacetamides (**1b**−**h)** bearing different substituents on both phenyl ring and nitrogen atom with NBS were examined (Table 2). All photoreactions of **1a**−**h** could afford the cyclization products, but both the proportion and the yields of

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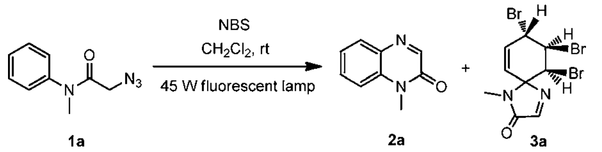
Table 1. Optimization of Photoreaction Conditions of **1a** with NBS[a]



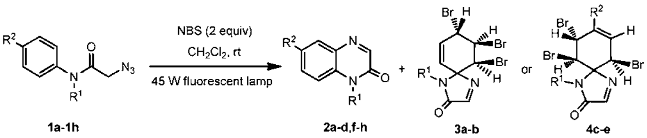
entry	equiv (NBS)	solvent	time (h)	conv[b] (%)	yield[c] (%) 2a	3a
1	1	CH_2Cl_2	6	60	82	11
2	1.5	CH_2Cl_2	6	83	83	12
3	2	CH_2Cl_2	3	99	85	9
4	2	CCl_4	10	80	70	8
5	2	CH_3COCH_3	15	50	50	6
6	2	CH_3CN	20	30	40	5

[a] Reaction conditions: compound **1a** (95 mg, 0.5 mmol) and NBS were dissolved in anhyd solvent (20 mL). The solution was irradiated with a household fluorescent lamp (45 W, $\lambda > 400$ nm) at ambient temperature under aerobic atmosphere. [b] Conversion based on **1a**. [c] Isolated yields based on consumed substrate.

products **2** and **3** were influenced by the substitutents. The photoreaction of **1b** gave products **2b** and **3b** in the similar proportion and yield to **1a** (entry 2), while for compounds **1c**,**d** bearing a halogen atom at the *para*-position of the phenyl ring, the reaction gave isomerized spirocycles **4c**,**d** besides main products **2c**,**d** (entries 3 and 4). When the *para*-substituent was changed to methyl group, as in the case of **1e**, a spirocyclic product **4e** was separated as the main product from the complex mixture after the reaction (entry 5). In contrast to **1a**–**d**, only the annulated products **2f**–**h** were produced from **1f**–**h** where a strong electron-attraction group like the nitro, cyano, or ethoxycarbonyl group was attached to the *para*-position (entries 6–8). Moreover, the photoreaction rate of **1f**–**h** increased greatly as compared with that of **1a**.

Unexpectedly, when compounds **1i**,**j** which bear an *o*-Cl or CO_2Me at the phenyl ring were subjected to the reaction conditions, spiro[cyclohexadien-1,2′-imidazol]-4,4′-diones (**5i**,**j**) were separated as the main products in moderate yields after reaction (Table 3, entries 1 and 2). Obviously, this group of products derived from an oxygen-mediated reaction. Similar products **5k** and **5k-1** were also obtained from the photoreaction of **1k** where a methoxy group was present at the *para*-position (Table 3, entry 3). All products **2**–**5** were fully identified by ^1H, ^{13}C NMR and HRMS, IR, and the stereochemistry of spirocyclic compounds was evaluated by means of NOESY. The structures of **3b** and **5j** were further confirmed by X-ray crystallography (see Supporting Information).

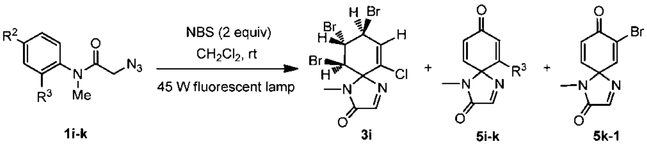
Table 2. NBS-Mediated Photoreactions of Substituted 2-Azido-*N*-phenylacetamides **1a**–**h**[a]



entry	substrate	R1	R2	time (h)	conv[b] (%)	yield[c] (%)			
1	**1a**	CH_3	H	3	99	**2a**	85	**3a**	9
2	**1b**	Ph	H	4	98	**2b**	77	**3b**	9
3	**1c**	CH_3	Br	2	99	**2c**	78	**4c**	9
4	**1d**	CH_3	Cl	2	99	**2d**	76	**4d**	8
5	**1e**	CH_3	CH_3	8	80			**4e**	50
6	**1f**	CH_3	NO_2	1	99	**2f**	90		
7	**1g**	CH_3	CN	1	99	**2g**	90		
8	**1h**	CH_3	CO_2Me	1.5	99	**2h**	88		

[a] Reaction conditions: compound **1** (0.5 mmol) and NBS (2.0 equiv) were dissolved in anhydrous DCM (20 mL). The solution was irradiated with a household fluorescent lamp (45 W, $\lambda > 400$ nm) at ambient temperature. [b] Conversions calculated on the basis of substrate. [c] Isolated yields based on the consumed substrate.

Table 3. NBS-Mediated Photoreactions of Substituted 2-Azido-*N*-phenylacetamides **1i**–**k**



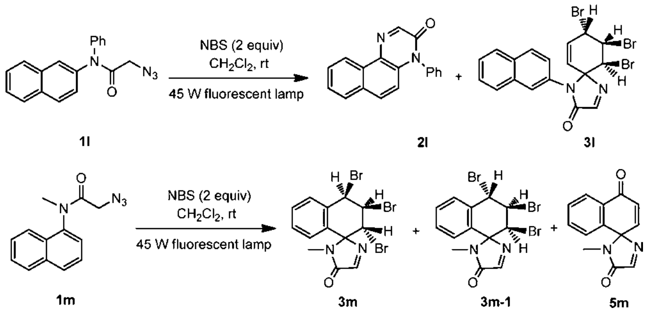
entry	substrate	R2	R3	time (h)	conv (%)	yield[a] (%)			
1	**1i**	H	Cl	3	91	**3i**	10	**5i**	48
2	**1j**	H	CO_2Me	2.5	92			**5j**	60
3	**1k**	OMe	H	1	99	**5k**	45	**5k-1**	25

[a] Isolated yields based on the consumed substrate.

For further extension, the photoreactions of two azido-*N*-naphthalenylacetamides (**1l**,**m**) were tested under the same conditions. As shown in Table 4, these two substrates behaved differently: for **1l**, both the annulated product (**2l**) and the spirocyclic product (**3l**) were produced; whereas only spirocyclization products were obtained after the photoreaction of **1m**. The structures of **2l** and **3l** were also confirmed by X-ray crystallography (see the Supporting Information).

On the basis of the results described above and the discussion about the photoreaction of NBS by Chow[15] and Kim,[16] a plausible mechanistic rationale for the formation of methylquinoxalin-2-ones (**2a**–**h**) and the spirocyclic compounds (**3a**,**b**, **4c**–**e**, and **5i**–**k**) is given in Scheme 2. Initially, the iminyl radical **8** is produced via the abstraction of α-hydrogen by bromine radical followed by nitrogen extrusion. Compound **8** then undergoes cyclization following either route a or route b to afford **9** or **10**. **9** is converted to **2** after aromatization. From **10** compounds **3**, **4**, and **5** are generated. The formation of **3** and **4** apparently involves the bromine atom abstraction from

Table 4. NBS-Mediated Photoreactions of Substituted 2-Azido-*N*-naphthylacetamides **1l**–**m**



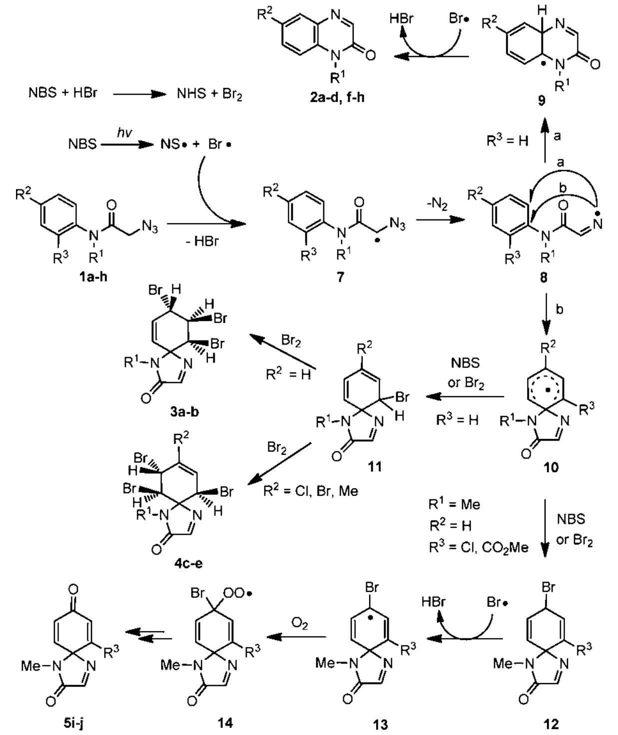
entry	sub	time (h)	conv (%)	yield^a (%)					
1	**1l**	7	85	**2l**	70	**3l**	15		
2	**1m**	15	80	**3m**	40	**3m-1**	30	**5m**	10

[a] Isolated yields based on the consumed substrate.

NBS or Br_2 followed by the addition of bromine molecule, while **5i** and **5j** are produced probably through intermediates **12**, **13**, and **14**. The oxygen atom in **5i** and **5j** is believed to come from oxygen, as the reactions were performed under the aerobic atomosphere.[17]

In summary, a simple and efficient synthesis of quinoxalin-2-ones or spiro[cyclohexene-1,2′-imidazol]-4′-ones has been developed by employing the reaction of **2**-azido-*N*-phenylacetamides with NBS under visible light irradiation at ambient temperature. These two kinds of products result from a free radical process involving the formation and cyclization of iminyl radicals. Notably, both the regioselectivity and the speed of the photocyclization are affected by the substituents attached to the phenyl ring. Detailed mechanism investigations and NBS-mediated photcyclization for the synthesis of other heterocycles are ongoing in our laboratory.

Scheme 2. Proposed Mechanism for the Formation of **2**–**5**



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Supporting Information Available. Experimental procedures, solubility data, spectroscopic data, ^1H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic data (CIF file) of **3b**, **5j**, **2l**, and **3l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For a detailed mechanistic discussion, see the Supporting Information.

The authors declare no competing financial interest.